means (e.g., cellular nucleophiles or enzymatic action) or preferably by means of an external signal (e.g., light or ultrasound).

As a second example, the bioconjugate contains a cytotoxic agent and is administered to a patient having psoriasis. In this example, a therapeutically effective amount of the bioconjugate is administered to an afflicted skin site. The cytotoxic agent is released by natural means or preferably by means of an external signal.

As a third example, the bioconjugate contains the enzymatic domain of diphtheria toxin (Nichols et al., 1997) and is administered to a patient having cancer. In this example, a therapeutically effective amount of the bioconjugate is administered intravenously to a patient such that the bioconjugate concentrates in the neoplastic cells. The enzymatic domain of diphtheria toxin is released from the bioconjugate by natural means (e.g., cellular nucleophiles or enzymatic action) or preferably by means of an external signal (e.g., light or ultrasound) and proceeds to kill the cancer cells.

As a fourth example, the bioconjugate contains an antisense oligonucleotide against hepatitis B virus (Yao et al., 1996; Madon and Blum, 1996) and is administered to a subject having hepatitis B. In this example, a therapeutically effective amount of the bioconjugate is administered intravenously to a patient such that the bioconjugate concentrates in the liver. The antisense oligonucleotide is released from the bioconjugate by natural means (e.g., cellular nucleophiles or enzymatic action) or preferably by means of an external signal (e.g., light or ultrasound) and proceeds to inhibit gene expression and replication of hepatitis B virus.

The present invention employs the following definitions:

Bioactive agent: any agent which is desired to be delivered to cells, tissues or organs for modulating or otherwise modifying cell function, including for therapeutic effects. In accordance with the present invention, bioactive agents include, but are not limited to, pharmaceutically active compounds or diagnostic compounds. Bioactive agents include, but are not limited to, peptides, oligopeptides, proteins, apoproteins, glycoproteins, antigens and antibodies or antibody fragments thereto, receptors and other membrane proteins, retro-inverso oligopeptides, protein analogs in which at least one non-peptide linkage replaces a peptide linkage, enzymes, coenzymes, enzyme inhibitors, amino acids and their derivatives, hormones, lipids, phospholipids, liposomes, ricin or ricin fragments; toxins such as aflatoxin, digoxin,

xanthotoxin, rubratoxin; antibiotics such as cephalosporins, penicillin and erythromycin; analgesics such as aspirin, ibuprofen and acetaminophen, bronchodilators such as theophylline and albuterol; beta-blockers such as propranolol, metoprolol, atenolol, labetolol, timolol, penbutolol and pindolol; antimicrobial agents such as those described above and ciprofloxacin, cinoxacin and norfloxacin; antihypertensive agents such as clonidine, methyldopa, prazosin, verapamil, nifedipine, aptopril and enalapril; cardiovascular agents including antiarrhythmics, cardiac glycosides, antianginals and vasodilators, central nervous system agents including stimulants, psychotropics, antimanics and depressants; antiviral agents; antihistamines such as chlorphenirmine and brompheniramine; cancer drugs including chemotherapeutic agents, such as chlorambucil, carboplatin, deratives of busulfan, doxorubicin, etoposide, topotecan (TPT); tranquilizers such as diazepam, chordiazepoxide, oxazepam, alprazolam and triazolam, anti-depressants such as fluoxetine, amitriptyline, nortriptyline and imipramine; H-2 antagonists such as nizatidine, cimetidine, famotidine and ranitidine, anticonvulsants; antinauseants; prostaglandins; muscle relaxants; anti-inflammatory substances; stimulants; decongestants; antiemetics; diuretics; antispasmodics; antiasthmatiics; anti-Parkinson agents; expectorants; cough suppressants, mucolytics; vitamins; and mineral and nutritional additives. Other molecules include nucleotides; oligonucleotides; polynucleotides; and their art-recognized and biologically functional analogs and derivatives including, for example, methylated polynucleotides and nucleotide analogs having phosphorothioate linkages; plasmids, cosmids, artificial chromosomes, other nucleic acid vectors; antisense polynucleotides including those substantially complementary to at least one endogenous nucleic acid or those having sequences with a sense opposed to at least portions of selected viral or retroviral genomes; promoters; enhancers; inhibitors; other ligands for regulating gene transcription and translation. In addition, the bioactive agent can be any other biologically active molecule that can form a conjugate with an organocobalt complex. The bioactive agent may further contain a spacer which provides a covalent bond with the cobalt atom of the organocobalt complex, but which does not adversely affect the biological activity of the bioactive agent.

Bioconjugate: a conjugate containing a bioactive agent and an organocobalt complex in which the bioactive agent is covalently bound directly to the cobalt atom or is covalenly bound indirectly to the cobalt atom via a spacer.

Non-reactive atom: an atom in the bioactive agent that will not lead to rearrangement or destruction of the bioactive agent under conditions of ligand exchange during receptor-mediated endocytosis, but that instead will reproduce the original form of the bioactive agent (or bioactive agent and spacer) and thereby unmask an active bioactive agent. The non-reactive atom may be a carbon atom, a nitrogen atom, an oxygen atom, a sulfur atom, a selenium atom or a silicon atom. A carbon atom (e.g. from an alkyl, acyl or aryl group) is particularly preferred. Such non-reactive atoms are also used in forming the covalent bond between the cobalt and the spacer.

Organocobalt complex: an organic complex containing a cobalt atom having bound thereto 4-5 calcogens as part of a multiple unsaturated heterocyclic ring system. In accordance with the present invention, suitable organocobalt complexes include, but are not limited to, cobalamin (coenzyme B_{12}), Co[SALEN] (which is a cobalamin analogue), organo(pyridine)-bis(dimethylglyoximato)cobalt, corrinoids (such as disclosed by Brown et al., 1996) and derivatives or analogues of any of the preceding, as well as pharmaceutically acceptable salts. The organocobalt complexes may be unsubstituted or substituted with conventional organic functional groups which will not alter the basic nature of the organocobalt complex. The basic nature of the organocobalt complex is to bind the bioactive agent covalently to the cobalt such that the cobalt-bioactive agent bond is readily cleavable as described herein. Examples of substituents which may be found on the organocobalt complex include amino, nitro, halogen (bromine, chlorine), sulfito, C_{2-6}-alkene and C_{2-6} alkyne. For example, the organocobalt complex can be formed having a nitro and/or halo (e.g., bromo) derivative of the corrin ring or having an extended conjugation with exocyclic olefin or alkylene groups. Other derivatives include cobalamin lactone, cobalamin lactame and those in which the benzimidiazole ring (e.g., of cobalamin, green corrinoid, and the like) are substituted with e.g., one or more halogen (bromine, chlorine), hydroxy or C_{1-6} alkyl. Such substituents are useful for increasing the λ_{max} to be used for cleavage of the bioconjugate as described herein. Further derivatives include anilide, ethylamide, mono-, di- or tri-carboxylic acid or proprionamide derivatives of cobalamin of Vitamin B_{12}. In one embodiment. the organocobalt complex is any organic complex conaining cobalt which is bound by transcobalamin and transported into a cell by a receptor-mediated process involving transcobalamin. In a second embodiment, the organocobalt complex may also be covalently bound directly or indirectly (through a spacer) to a targeting molecule, wherein said targeting molecule is bound by its receptor and the complex is transported into a